Critical Care

LETTER

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Letter to the editor regarding Latent class analysis to predict intensive care outcomes in Acute Respiratory Distress Syndrome: a proposal of two pulmonary phenotypes

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To the editor,

With great interest we read the manuscript Latent class analysis to predict intensive care outcomes in Acute Respiratory Distress Syndrome: a proposal of two pulmonary phenotypes by Wendel Garcia et al. [1].

The authors have developed a proposal of two ARDS phenotypes based on a statistical method analyzing respiratory mechanics, gas-exchange and CT-derived gas-and tissue volume: Patients with *non-recruitable* phenotype 1 present with a lower respiratory system elastance, dead space and total lung tissue, as well as a higher PaO2/FiO2 ratio, a more physiological pH and a less inhomogeneous lung with a lower proportion of potentially recruitable lung than *recruitable* phenotype 2. Results showed that ICU mortality rate was higher in the *recruitable* than the *non-recruitable* phenotype even when corrected for PaO2/FiO2 ratio. The authors compare their newly developed phenotypes to other previously developed phenotypes (hypo-and hyper-inflammatory phenotypes) and they state that, although there was no direct correlation between the different phenotypes, there were some associations between high recruitability, and pulmonary inhomogeneity and the presence of increased pulmonary inflammatory biomarkers.

We acknowledge the authors for their effort in trying to develop personalized mechanical ventilation for ARDS, however we feel that they have artificially developed phenotypes based on a statistical method rather than on the pathophysiology of ARDS.

ARDS is characterized by an increased permeability of the alveolar-capillary barrier resulting in lung edema with protein-rich fluid causing an impairment of arterial oxygenation. Lung edema, endothelial and epithelial injury are accompanied by an influx of activated neutrophils into the interstitium and broncho-alveolar space [2, 3]. This increased permeability of the alveolar-capillary barrier combined with fluid filtration rates exceeding the capacity of the lung lymphatics for fluid removal leads to alveolar flooding, a major cause of hypoxemia in ARDS. Flooded lung units contribute to ventilation–perfusion mismatch and intrapulmonary shunt, all influencing lung recruitability.

The proposed phenotypes are artificially created phenotypes based on the same pathophysiological process. Mortality difference between both phenotypes is likely caused by the host's reaction on the underlying inflammatory response. Since classification should serve clarification and guide therapy we see no additional value in another phenotype as it does not change our approach to the problem. Mechanical ventilation should already be personalized since it is depending on many different patient parameters. It would be far more promising

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to examine phenotypes based on the inflammatory response, since treatment based on the pathophysiology of ARDS will be likely the way to go [4].

Response to: Letter to the editor regarding Latent class analysis to predict intensive care outcomes in Acute Respiratory Distress Syndrome: a proposal of two pulmonary phenotypes

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We thank Dr. van Wessem and Dr. Leenen for their interest in our manuscript [1] and for their comments in response to it.

Since its coining in 1967, insights into the acute respiratory distress syndrome (ARDS) have evolved concurrent to the realization that the pathophysiological pathway, as described by Drs. van Wessem and Leenen, is an oversimplification of the heterogeneity governing ARDS. Neither do all patients with ARDS present histopathological signs of pneumonia with a high influx of activated neutrophils, as suggested by Drs. van Wessem and Leenen, nor do all lungs present diffuse alveolar damage (DAD) [5]. Considering this pathophysiological heterogeneity and the definition of a phenotype as *a clinical entity defined by observable characteristics without any mechanistic pathophysiological implication*, the claim by Drs. van Wessem and Leenen, that we "have artificially developed phenotypes based on a statistical method rather than on the pathophysiology of ARDS", is rather surprising.

Drs. van Wessem and Leenen argue that the "mortality difference between both phenotypes is likely caused by the host's reaction on the underlying inflammatory response ". Indeed the leading cause for mortality in ARDS, and consistently in the *hyper-inflammatory* phenotype, is severe sepsis and shock [5]. However, in patients presenting with DAD, concurrent to our *recruitable* phenotype, the cause of mortality is therapy refractory hypoxemia [6]. Notably, DAD presenting patients do not stand out due to their systemic inflammation or multiorgan dysfunction, but by a low PaO_2/FiO_2 ratio and compliance, defining characteristics of our *recruitable* phenotype [6]. In fact, the alveolar concentration of most inflammatory mediators significantly surpasses their plasma concentration in ARDS, indistinctively of the underlying inflammatory phenotype, suggesting that the "currently known [inflammatory] phenotypes do not reflect the alveolar host response" [7].

Drs. van Wessem and Leenen conclude that "mechanical ventilation should already be personalized since it is depending on many different patient parameters". Nonetheless, exactly the complex interaction of viscoelastic properties and host response, broadly correlating with the lungs morphological presentation, have impeded the successful personalization of mechanical ventilation [8]. To resolve this conundrum, identification of phenotypes reflecting the mechanical and morphological properties of the lung, like our proposed phenotypes, are necessary.

In conclusion, Drs. van Wessem and Leenen seem to neglect that ARDS is a syndrome of primarily pulmonary expression, and while we agree on the promise of inflammatory phenotypes to tailor systemic immunomodulating therapies, the cornerstone of ARDS management remains mechanical ventilation. Personalized research considering predictive enrichment through pulmonary focused phenotypes, such as our proposed *non-recruitable* and *recruitable* phenotypes, is of eminent importance to accomplish truly "individualized" mechanical ventilation.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
All authors declare that they have no conflict of interest.

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References
1. Wendel Garcia PD, Caccioppola A, Coppola S, et al. Latent class analysis to predict intensive care outcomes in Acute Respiratory Distress Syndrome: a proposal of two pulmonary phenotypes. Crit Care. 2021;25(1):154. https://doi.org/10.1186/s13054-021-03578-6
2. Grommes J, Soehnlein O. Contribution of neutrophils to acute lung injury. Mol Med. 2011;17(3–4):293–307. https://doi.org/10.2119/molmed.2010.00138.
3. Leliefeld PH, Wessels CM, Leenen LP, Koenderman L, Pillay J. The role of neutrophils in immune dysfunction during severe inflammation. Crit Care. 2016;23(20):73. https://doi.org/10.1186/s13054-016-1250-4.
4. Kitsios GD, Yang L, Manatakis DV, Nouraie M, Evankovich J, Bain W, Dunlap DG, Shah F, Barbash IJ, Rapport SF, Zhang Y, DeSensi RS, Weathington NM, Chen BB, Ray P, Mallampalli RK, Benos PV, Lee JS, Morris A, McVerry BJ. Host-response subphenotypes offer prognostic enrichment in patients with or at risk for acute respiratory distress syndrome. Crit Care Med. 2019;47(12):1724–34. https://doi.org/10.1097/CCM.0000000000004018.
5. Cardinal-Fernández P, Lorente JA, Ballén-Barragán A, Matute-Bello G. Acute respiratory distress syndrome and diffuse alveolar damage new insights on a complex relationship. Ann Am Thorac Soc. 2017;14(6):844–50.

6. Lorente JA, Cardinal-Fernández P, Muñoz D, et al. Acute respiratory distress syndrome in patients with and without diffuse alveolar damage: an autopsy study. Intensive Care Med. 2015;41(11):1921–30.
7. Heijnen NFL, Hagens LA, Smit MR, et al. Biological subphenotypes of acute respiratory distress syndrome may not reflect differences in alveolar inflammation. Physiol Rep. 2021;9(3):e14693.
8. Constantin J-M, Jabaudon M, Lefrant J-Y, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. Lancet Respir Med. 2019;7(10):870–80.

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